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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/911,821	07/24/2001	Phillip S. Pang	A33723 / 070050.1407	6323

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EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 07/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/911,821	PANG ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-62* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,11,12,14-20,22-33,40,41,43-49,51-54 and 57-62* is/are rejected.

7)☒ Claim(s) *5-10,13,21,34-39,42,50,55 and 56* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 5 sheets
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Election/Restrictions

Applicant's election without traverse of Group I (claims 1-60) and election of Species C (claims 30-50) in the reply filed on 28 April 2005 is acknowledged.

Upon further consideration, the previous restriction and species election requirement, mailed 24 March 2005, has been withdrawn by the Examiner. Groups I and II are rejoined and claims 1-62 are currently under examination.

Information Disclosure Statement

The information disclosure statement filed 26 December 2001 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because the title was not provided for a majority of the listed documents. It has been placed in the application file, but documents lined through by the examiner have not been considered as to the merits unless cited on the PTO-892 form. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. See for example paragraphs 000147, line 5, 000149, line 9, 000151, line 5, 000155, line 3, 000156, line 4, and 000159, line 3. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 11, 12, 14, 19, 22, 23, 27, 30-33, 40, 41, 43, and 48 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Barrett et al.

The instant claims are drawn to methods for predicting intramolecular and intermolecular biopolymer interactions comprising obtaining genomic/biopolymeric sequence data, subjecting said sequence data to an alignment process, subjecting sequence alignment data to a combinatorial matching process, preparing a set of actual frequency tables and scoring said tables, and a screening process involving a the steps of a standardization process, a threshold determination process and a chain elimination process.

[Claim 1-3, 22, 23, 27, and 30-32]: Barrett et al. set forth methods for analyzing statistical sequence comparison techniques and using log-odds scoring techniques as a means of evaluating the statistical probabilities by comparison to a null hypothesis. See Barrett et al., Page 1, column 1, lines 1-10. Examples are provided wherein the disclosed methodology is performed on three separate families of protein with known intermolecular binding properties. See Barrett et al., page 5, column 1, line 20 through page 2, column 2, line 32. Barrett et al. apply a linear hidden Markov model (HMM) to the analysis of various sequence alignments on the basis of a simple sequence alignment (broadly construed to read on an actual frequency table as provided in the specification, paragraph 0052) and consideration of sequence gaps (broadly construed to read on chain elimination). See Barrett et al., Figure 1 and page 2, first column, line 22 through column 2, line 10. Following this, the models are augmented with the addition of Free Insertion Modules (FIMs) at the end and provide for a better sequence match. See Barret et al., page 2, column 2, lines 11-23. Following the construction of an HMM for a given family of protein sequences, a sequence alignment and modeling (SAM) suite is employed to the negative log likelihood scores that classify and rank sequence alignments. See Barret et al., page 2, column 2, lines 24-31. Further, a Z-score method is utilized by the SAM suite to normalize alignment data and broadly construed to read on a standardization process wherein the results are uniformly scaled. See Barrett et al., page 2, column 2, line 32-47. Barrett et al. clearly establish that within the context of the SAM, a variety of bull models and suitable thresholds are considered in the disclosed method. See Barrett et al., page 1, column 1, lines 11-20

and page 3, column 1, line 2 through page 4, column 1, line 36. The generation of alignments utilizing a null hypothesis are broadly construed to read on an expected frequency table as provided for in paragraph 0053 of the instant specification.

[Claims 4 and 33]: Barrett et al. provide for a threshold determination process for determining false negatives from false positives, wherein threshold function is established on sequence length, composition, estimates of sequence conservation and an establishes a standard deviation score, σ (broadly construed to be a threshold determined on the measured basis of location and dispersion). See Barrett et al., page 5, column 2, lines 21-42.

[Claims 11 and 40]: The threshold process set forth by Barrett et al. was performed on the basis of shared, common positions and provided for an ideal discrimination method for good null hypothesis models that showed little variation. See Barrett et al., Figure 2 and page 5, column 2, lines 21 through page 6, column 2, line 9.

[Claim 12, 14, 19, 41, 43, and 48]: The SAM suite returns negative log likelihood scores (NLL), -log(P(s|m)), on the basis of the probability that a given sequence s was generated by the model m. Further, the SAM suite utilizes the Z-score method to provide for a normalized NLL score. See Barrett et al., page 2, column 2, lines 24-46.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 1-4, 11, 12, 14, 15, 17-19, 22-27, 30-33, 40, 41, 43, 44, 46-48, 54, 57 and 58 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barrett et al. in view of Agresti (See IDS: Agresti 1996).

The instant claims are drawn to methods for predicting intramolecular and intermolecular biopolymer interactions comprising obtaining genomic/biopolymeric sequence data, subjecting said sequence data to an alignment process, subjecting sequence alignment data to a combinatorial matching process, preparing a set of actual frequency tables and scoring said tables, and a screening process involving a the steps of a standardization process, a threshold determination process and a chain elimination process. The instant claims further provide for the use of specific equations and statistical methods in predicting intramolecular and intermolecular biopolymer interactions.

[Claims 15, 18, 24-26, 44, 46, 47, 54, 57 and 58]: As described above, Barrett et al. set forth methods for analyzing statistical sequence comparison techniques and using log-odds scoring techniques as a means of evaluating the statistical probabilities by comparison to a null hypothesis and applies a linear hidden Markov model (HMM) to the analysis of various sequence alignments on the basis of a simple sequence alignment and consideration of sequence gaps. However, Barrett et al. does not fairly teach the use of the instantly claimed equations in scoring and estimating the values of an expected frequency table or comparing estimated and actual frequency tables.

Agresti sets forth methods and statistical approaches that are generally applicable for use in systems where the null hypothesis is applied. See Agresti, page

27, line 30 through page 28, line 7. Agresti teaches the use of the instantly claimed equations for estimating expected frequencies and determining a test for independence relying on Pearson statistics. See Agresti, equation 2.4.3 and page 30, lines 4-28. Further, Agresti teaches the instantly claimed equation and statistical approach for the use of residuals as applied to testing against the null hypothesis. See Agresti, page 31, line 19 through page 32, line 24. Agrsti also teaches that a residual value above 2 in absolute value indicates a lack of fir of the null hypothesis for a given cell. Agresti further teaches statistical analyses that rely on the use of sparse data tables for P scores. See Agresti, page 194, lines 1-20.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the statistical methods and equations, as taught by Agresti, with the statistical sequence comparison techniques set forth by Barrett et al. because Aresti provides a better model fitting the null hypothesis.

Claims 1-4, 11, 12, 14-19, 22-27, 30-33, 40, 41, 43, 44-48, 54, 57 and 58 rejected under 35 U.S.C. 103(a) as being unpatentable over Barrett et al. in view of Agresti as applied to claims 1-4, 11, 12, 14, 15, 17, 18, 19, 22-27, 30-33, 40, 41, 43, 44, 46-48, 54, 57 and 58 above, and further in view of Duffy in view of Efron.

[Claim 16 and 45]: As described above, Barrett et al. set forth methods for analyzing statistical sequence comparison techniques and using log-odds scoring techniques as a means of evaluating the statistical probabilities by comparison to a null

hypothesis. However, Barrett et al. does not fairly teach the use of the instantly claimed equations in scoring and estimating the values of an expected frequency table. Agresti sets forth methods and statistical approaches, such as estimated exact statistical methods, that are generally applicable for use in systems where the null hypothesis is applied. However neither Barrett et al. not Agresti fairly teaches the use of an estimated-exact statistical method based on a monte carlo simulation of a distribution.

Duffy sets forth statistical methods that are generally applicable for use in systems where the null hypothesis is applied and sets teaches the specific application of a jackknife-type perturbation scheme. See Duffy, page 158, column 1, line 8 through page 160, column 2, line 23. However, Duffy does not fairly teach that a jackknife-type perturbation scheme is based on a monte carlo simulation of a distribution.

Efron sets for the several nonparametric statistical methods wherein the a monte carlo simulation is applied to a jackknife sytatical method. See Efron, Table 1 and page 589 line 1 through page 591, line 11.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to an estimated-exact statistical method based on a monte carlo simulation as taught by Duffy in view of Efron, for use the statistical methods and equations, as taught by Agresti, with the statistical sequence comparison techniques set forth by Barrett et al. because Agresti, in further view of Duffy in view of Efron, provides for a better model fitting the null hypothesis.

Claims 1-4, 11, 12, 14, 19, 20, 22, 23, 27-29, 30-33, 40, 41, 43, 48, and 49 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barrett et al. in view of Press et al. (See IDS: Press et al. 1988-1997).

The instant claims are drawn to methods for predicting intramolecular and intermolecular biopolymer interactions comprising obtaining genomic/biopolymeric sequence data, subjecting said sequence data to an alignment process, subjecting sequence alignment data to a combinatorial matching process, preparing a set of actual frequency tables and scoring said tables, and a screening process involving a the steps of a standardization process, a threshold determination process and a chain elimination process. The instant claims further provide for the use of specific equations and statistical methods in predicting intramolecular and intermolecular biopolymer interactions.

[Claims 20, 28, 29 and 49]: As described above, Barrett et al. set forth methods for analyzing statistical sequence comparison techniques and using log-odds scoring techniques as a means of evaluating the statistical probabilities by comparison to a null hypothesis and applies a linear hidden Markov model (HMM) to the analysis of various sequence alignments on the basis of a simple sequence alignment and consideration of sequence gaps. However, Barrett et al. does not fairly teach the use of Cramer's V statistic and the instantly claimed equations in a scoring process.

Press et al. sets forth methods and statistical approaches that are generally applicable for use in systems where the null hypothesis is applied. See Press et al., page 630, lines 1-17. Press et al. teaches the use of the instantly claimed equations for

use in establishing association significance. See Press et al., page 630, line 12 through page 631, line 23.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to use the statistical methods and equation, as taught by Press et al., with the statistical sequence comparison techniques set forth by Barrett et al. because Press et al. provides a better model fitting the null hypothesis.

Claims 1-4, 11, 12, 14, 19, 22, 23, 27, 30-33, 40, 41, 43, 48, 51-53, and 59-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barrett et al. in view of Toll et al.

The instant claims are drawn to methods for predicting intramolecular and intermolecular biopolymer interactions comprising obtaining genomic/biopolymeric sequence data, subjecting said sequence data to an alignment process, subjecting sequence alignment data to a combinatorial matching process, preparing a set of actual frequency tables and scoring said tables, and a screening process involving a the steps of a standardization process, a threshold determination process and a chain elimination process. The instant claims further provide for the steps of subjecting actual frequency tables to a misalignment process to produce misaligned sequence information, using the misaligned information to realign sequences to produce a second set of sequence alignment data, and then repeating all previous steps using the second set of sequence alignment data to predict intramolecular and intermolecular interactions.

[Claims 51, 52, and 59-62]: As described above, Barrett et al. set forth methods for analyzing statistical sequence comparison techniques and using log-odds scoring techniques as a means of evaluating the statistical probabilities by comparison to a null hypothesis and applies a linear hidden Markov model (HMM) to the analysis of various sequence alignments on the basis of a simple sequence alignment and consideration of sequence gaps. However, Barrett et al. does not fairly teach the steps involving a misalignment process that produces misaligned sequence information or using the misaligned sequence information to realign sequences in order to produce a second set of sequence alignment data for use in the disclosed method.

Toll et al. sets forth methods and systems for comparing and characterizing biological sequence data involving matching between segments of sequences at defined positions. The disclosed method includes probabilistic models, such as the hidden Markov model, and is designed as a networked series of modules and operates in a recursive fashion. See Toll et al., paragraphs 0008-0013. One embodiment includes a third module that explicitly accounts for similarity and dissimilarity between regions of each sequence of a given alignment set. See Toll et al., at least paragraphs 0014 and 0017.

[Claim 53]: Toll et al. provides for an alternative embodiment of the method wherein a module evaluates and identifies alignment sets which return values that exceed a threshold. Each set includes a first sequence from sequences of a first species and a second sequence from sequences of a second species. Additional sequences can be included in each set. The evaluating includes: (i) comparing the first

and second sequence of each set to identify similar and dissimilar segments; and (ii) returning a value indicative of the match between the similar and dissimilar segments of the set and a defined pattern of similarity and dissimilarity. See Toll et al., at least paragraph 0020.

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to employ similarity and dissimilarity in the alignment between sequences, as taught by Toll et al., in combination with the sequence comparison methodology as taught by Barrett et al. because Toll et al. provides an enhanced analysis and evaluation of aligned sequences.

Allowable Subject Matter

Claims 5-10, 13, 21, 34-39, 42, 50, 55, and 56 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D. can be reached on (571) 272-0718. The fax phone

number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (571) 272-0549.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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EDJ EDJ

7 July 2005

JOHN S. BRUSCA, PH.D
PRIMARY EXAMINER